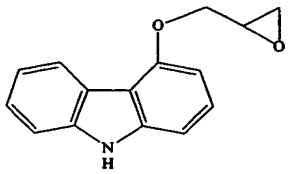
CLAIMS

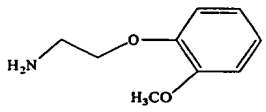
What is claimed is:

1. A process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,



II

with a compound of formula III, 2-(2-methoxyphenoxy)ethylamine



III

wherein the compound of formula III is at a molar excess over the compound of formula II.

2. The process of claim 1, wherein the compound of formula III and the compound of formula II are at a molar ratio from about 1.5:1 to about 100:1.

3. The process of claim 1, wherein the compound of formula III and the compound of formula II are at a molar ratio from about 2.8:1 to about 10:1.

4. The process of claim 1, wherein the compound of formula III and the compound of formula II are at a molar ratio from about 2.8:1 to about 6:1.

5. The process of claim 1, wherein the reacting step is performed in a solvent.

6. The process of claim 5, wherein the solvent is selected from the group consisting of

toluene, xylene and heptane.

7. The process of claim 1, wherein the reacting step is performed in a solvent mixture wherein the solvent mixture comprises multiple solvents.

8. The process of claim 7, wherein a solvent of the solvent mixture is selected from the group consisting of toluene, xylene and heptane.

9. The process of claim 1, wherein the reacting step is performed at a temperature from about 25°C to about 150°C.

10. The process of claim 1, wherein the reacting step is performed at a temperature from about 60°C to about 120°C.

11. The process of claim 1, wherein the reacting step is performed under neat conditions.

12. The process of claim 11, wherein the neat conditions are obtained by melting a solid form of the compound of formula III to form a liquid and, dissolving the compound of formula II in the liquid to form a reaction mixture.

13. The process of claim 11, further comprising a step of reducing the temperature of the reaction mixture after dissolving the compound of formula II.

14. The process of claim 13, wherein the temperature is reduced to about 70°C.

15. The process of claim 11, further comprising a step of adding an organic solvent: water mixture to the reaction mixture.

16. The process of claim 15, wherein the organic solvent is selected from the group consisting of ethyl acetate, butyl acetate and methyl ethyl ketone.

17. The process of claim 15, further comprising a step of adjusting the pH of the organic solvent: water mixture to the reaction mixture after the organic solvent: water mixture is added to the reaction mixture.

18. The process of claim 17, wherein the pH is adjusted to less than about pH 5.

19. The process of claim 17, wherein the pH is adjusted from about pH 3 to about pH 5.

20. The process of claim 11, further comprising steps of:

a) isolating carvedilol hydrochloride after adjusting the pH, and

b) purifying carvedilol.

21. The process of claim 20, wherein carvedilol hydrochloride is a hydrate.

22. Crystalline carvedilol hydrate.

23. Crystalline carvedilol.

24. Crystalline carvedilol (methyl-ethyl-ketone) solvate.

25. Crystalline carvedilol Form III.

26. The crystalline carvedilol of claim 25, characterized by an X-ray powder diffraction pattern having peaks at about 8.4 ± 0.2, 17.4 ± 0.2, and 22.0 ± 0.2 degrees two-theta.

27. The carvedilol of claim 26, further characterized by an X-ray powder diffraction pattern having peaks at about 9.3 ± 0.2, 11.6 ± 0.2, 13.2 ± 0.2, 13.5 ± 0.2, 14.2 ± 0.2, 15.3 ± 0.2, 15.8 ± 0.2, 18.4 ± 0.2, 19.4 ± 0.2, 20.6 ± 0.2, 21.4 ± 0.2, 26.5 ± 0.2 and 27.6 ± 0.2 degrees two-theta.

28. The crystalline carvedilol of claim 24, characterized by a water content of about 2.0 % by weight.

29. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline carvedilol of claim 24, and a pharmaceutically acceptable carrier.

30. A method for treating a patient suffering from congestive heart failure by administering a therapeutically effective amount of crystalline carvedilol Form III.

31. A method for treating a patient suffering from hypertension by administering a therapeutically effective amount of crystalline carvedilol Form III.

32. Crystalline carvedilol Form IV.

33. The crystalline carvedilol of claim 32, characterized by an X-ray powder diffraction pattern having peaks at about 11.9 ± 0.2, 14.2 ± 0.2, 18.3 ± 0.2, 19.2 ± 0.2, 21.7 ± 0.2,

and 24.2 ± 0.2 degrees two-theta.

34. The crystalline carvedilol of claim 33, further characterized by an X-ray powder diffraction pattern having peaks at about 15.7 ± 0.2, 16.5 ± 0.2, 17.7 ± 0.2, 19.6 ± 0.2, 22.2 ± 0.2, 23.9 ± 0.2, 24.9 ± 0.2, 27.4 ± 0.2 and 28.2 ± 0.2 degrees two-theta.

35. Crystalline carvedilol (methyl-ethyl-ketone) solvate Form V.

36. The crystalline carvedilol of claim 35, characterized by an X-ray powder diffraction pattern having peaks at about 4.1 ± 0.2, 10.3 ± 0.2, and 10.7 ± 0.2 degrees two-theta.

37. The crystalline carvedilol of claim 36, further characterized by an X-ray powder diffraction pattern having peaks at about 11.5 ± 0.2, 12.6 ± 0.2, 14.0 ± 0.2, 14.8 ± 0.2, 15.4 ± 0.2, 16.4 ± 0.2, 16.8 ± 0.2, 18.8 ± 0.2, 20.8 ± 0.2, 21.1 ± 0.2, 21.6 ± 0.2, and 25.4 ± 0.2 degrees two-theta.

38. The crystalline carvedilol of claim 35, characterized by a methyl-ethyl-ketone content of about 14 % by weight.

39. Carvedilol HCl Hydrate.

40. The crystalline carvedilol of claim 39, characterized by an X-ray powder diffraction pattern having peaks at about 6.5 ± 0.2, 10.2 ± 0.2, 10.4 ± 0.2, 15.8 ± 0.2,16.4 ± 0.2 and 22.2± 0.2 degrees two-theta.

41. The crystalline carvedilol of claim 40, further characterized by an X-ray powder diffraction pattern having peaks at about 14.2 ± 0.2, 14.7 ± 0.2, 16.4 ± 0.2, 17.7 ± 0.2, 20.0 ± 0.2, 21.5 ± 0.2, 21.9 ± 0.2, 22.9 ± 0.2, 25.2 ± 0.2, 25.3 ± 0.2, 27.2 ± 0.2, 27.4 ± 0.2, 28.2 ± 0.2, 28.6 ± 0.2, 29.6 ± 0.2 degrees two theta.

42. The crystalline carvedilol of claim 39 characterized by a water content of about 3.5% by weight.

43. A method for preparing crystalline carvedilol Form I, comprising the steps of:

a) dissolving carvedilol in a solution by heating;

b) heating the solution until the crystalline carvedilol is completely dissolved;

c) reducing the temperature of the solution;

d) agitating the solution for a period of time;

d) further reducing the temperature of the solution;

e) further agitating the solution for a period of time; and,

e) collecting crystalline carvedilol Form I.

44. The method of claim 43, wherein the dissolving step is performed by heating the solution to about 77°C.

45. The method of claim 43, wherein the step of reducing the temperature of the solution is performed by cooling the solution to about 50° C in a time period of about 15 min.

46. The method of claim 43, wherein the step of agitating the solution is performed at about 50° C for about 48 hours.

47. The method of claim 43, wherein the step of further reducing the temperature of the solution is performed by cooling the solution to about 10°C in about 0.75 hours with agitation.

48. The method of claim 43, wherein the step of further agitating the solution is performed by stirring the suspension for more than about 5 hours.

49. A method for preparing crystalline carvedilol Form II, comprising the steps of:

a) forming a solution of carvedilol by dissolving carvedilol in a solvent;

b) precipitating carvedilol Form II by cooling the solution; and,

c) isolating crystalline carvedilol Form II.

50. The process of claim 49, wherein the temperature is from about 40° C to about the boiling temp of the solvent.

51. The process of claim 49, wherein the precipitated carvedilol Form II is isolated by filtration

52. The process of claim 49, wherein the solution is cooled to a temperature from about -20°C to ambient temperature.

53. The process of claim 49, wherein the solvent is selected from the group consisting of methanol, ethanol, 1-propanol, isopropanol, n-butanol, ethylene glycol, butyl acetate, isobutyl methyl ketone, dichloromethane, dichloroethane, acetonitrile, acetone, isoamylalcohol, xylene and toluene.

54. A method for preparing crystalline carvedilol Form II, comprising the steps of:

a) forming a solution of carvedilol by dissolving carvedilol in a solvent mixture;

b) precipitating carvedilol Form II by cooling the solution to about -20°C; and,

c) isolating crystalline carvedilol Form II.

55. The process of claim 54, wherein the temperature of the solution is from about 40°C to about the boiling temperature of the solvent.

56. The process of claim 54, wherein the precipitated carvedilol Form II is isolated by filtration.

57. The process of claim 54, wherein the solution is cooled to a temperature from about -20°C to ambient temperature.

58. The method of claim 54, wherein the solvent mixture is selected from the group consisting of acetone: cyclohexane, chloroform: cyclohexane, dichloroethane: cyclohexane, dichloromethane: cyclohexane, pyridine: cyclohexane, tetrahydrofurane:cyclohexane, dioxane: cyclohexane, acetone: hexane, chloroform: hexane, dichloroethane: hexane, dichloromethane: hexane, tetrahydrofuran: hexane and ethanol: hexane.

59. A method for preparing crystalline carvedilol Form III, comprising the steps of:

a) dissolving carvedilol in a solvent to form a solvent solution; and,

b) precipitating crystalline carvedilol Form III from the solvent solution using

water as an anti-solvent.

60. The method of claim 59, wherein water is present in the solvent solution during the dissolving step.

61. The method of claim 59, wherein the precipitation step is performed by adding water to the solution after carvedilol is fully dissolved in the solvent.

62. The method of claim 59, wherein the dissolving step is performed at elevated temperature.

63. The method of claim 59, wherein the elevated temperature is from about 40° C to about 90° C.

64. The method of claim 59, wherein the elevated temperature is about 55 °C.

65. The method of claim 59, wherein the dissolving step is performed at ambient temperature.

66. The method of claim 59, wherein the solvent is selected from the group consisting of pyridine, dioxane, methanol, ethanol, isopropanol and chloroform.

67. The method of claim 59, wherein the solvent consists of a mixture of solvents.

68. A method for preparing crystalline carvedilol Form IV, comprising the steps of:

a) dissolving carvedilol in a solvent to form a solvent solution;

b) adding an anti-solvent to the solvent solution; and,

c) precipitating crystalline carvedilol Form IV from the solvent solution.

69. The method of claim 68, wherein the solvent is methyl ethyl ketone.

70. The method of claim 68, wherein the anti-solvent is cyclohexane.

71. The method of claim 68, wherein the dissolving step is performed at from about 10°C to about 50 °C.

72. The method of claim 68, wherein the dissolving step is performed at about 55 °C.

73. The method of claim 68, wherein the dissolving step is performed at ambient

temperature.

74. A method for preparing crystalline carvedilol Form V, comprising the steps of:

a) dissolving carvedilol in a solvent to form a solvent solution; and,

b) precipitating and isolating crystalline carvedilol Form V from the solvent solution.

75. The method of claim 74, wherein the solvent is methyl ethyl ketone.

76. The method of claim 74, wherein the dissolving step is performed by dissolving carvedilol at ambient temperature.

77. The method of claim 74, wherein the temperature of dissolution is from about 10° C to about 80° C.

78. The process of claim 74, wherein carvedilol Form V is precipitated by cooling.

79. A method for preparing crystalline carvedilol Form V, comprising the steps of:

a) dissolving carvedilol in a solvent to form a solvent solution; and,

b) precipitating and isolating crystalline carvedilol Form V from the solvent solution

wherein the precipitation step is performed by adding an anti-solvent.

80. The method of claim 79, wherein the solvent is methyl ethyl ketone.

81. The method of claim 79, wherein the dissolving step is performed by dissolving carvedilol at ambient temperature.

82. The method of claim 79, wherein the of anti-solvent is hexane.